CHAPTER 17

Prostate cancer

Judd W. Moul, MD, FACS, Kenneth J. Pienta, MD, Brent K. Hollenbeck, MD, and Michael E. Ray, MD, PhD

Prostate cancer is the most common cancer in American men. Despite the fact that this cancer will be diagnosed in an estimated 232,090 American men in the year 2005 and will lead to the death of approximately 30,350 men, there is no universally agreed-upon strategic plan for its diagnosis and management.

Epidemiology

Age The risk of developing prostate cancer begins to increase at age 50 years in white men who have no family history of the disease and at age 40 years in black men and those who have a first-degree relative (father, brother) with prostate cancer. Risk increases with age, but, unlike other cancers, prostate cancer has no "peak" age or modal distribution. There has been a downward "age migration" in the PSA (prostate-specific antigen) era such that the median age of diagnosis is now approximately 60 years old.

Race The highest incidence of prostate cancer in the world is found in American black men, who have approximately a 9.8% lifetime risk of developing this cancer. This rate is slightly higher than the 8% lifetime risk for American white men. Black men have an incidence of prostate cancer that is 1.6 times that of whites.

The Japanese and mainland Chinese populations have the lowest rates of prostate cancer. Interestingly, although Japanese immigrants to the United States have a higher incidence of prostate cancer than Japanese people living in Japan, their rate is still about half that of American whites.

Socioeconomic status appears to be unrelated to the risk of prostate cancer, and the explanation for racial variability is unknown. However, an interplay of diet, hormonal factors, and genetics likely acounts for the variability.

Geography The incidence of prostate cancer is highest in Scandinavian countries (22 cases per 100,000 population) and lowest in Asia (5 per 100,000). Risk may be inversely related to ultraviolet light exposure, as the incidence increases the farther one lives from the equator. However, recent studies show extremely high rates in populations of African heritage, such as Jamaicans.

Etiology and risk factors

Family history Men who have a first-degree relative with prostate cancer have approximately a twofold increased risk of developing prostate cancer during their lifetime. An individual who has two first-degree relatives with prostate cancer has a ninefold increase in lifetime risk.

True hereditary prostate cancer occurs in a small number of men and tends to develop at a early age (< 55 years old).

Dietary fat Studies have suggested that dietary fat may increase the risk of prostate cancer. However, no definitive proof of its role has yet been found.

Vasectomy Several large epidemiologic studies suggest that vasectomy may increase the relative risk of prostate cancer by as much as 1.85. However, these same studies do not report an increased risk of dying from prostate cancer associated with vasectomy but do indicate a statistically increased risk of dying from *lung* cancer. These findings argue against an association between vasectomy and prostate cancer. Currently, this association is unproven and does not constitute grounds for fundamental changes in the use of vasectomy.

Sexual activity/sexually transmitted disease There is limited association between sexual activity in a man or sexually transmitted diseases and the incidence of prostate cancer.

Sexual activity has been hypothesized as a possible risk factor for prostate cancer, but a large prospective study by Leitzmann et al may finally provide an answer to this question. In the Health Professionals Follow-up Study, 29,342 men aged 46 to 81 years provided information on their history of ejaculation frequency by filling out serial questionnaires over 8 years. This history was compared with the incidence of prostate cancer in the group. Overall, most categories of ejaculatory frequency were unrelated to the risk of prostate cancer. Only high ejaculation frequency (greater than 21 ejaculations per month) was associated with a decreased risk of prostate cancer, with a lifetime relative risk of 0.67 *(Leitzmann MF, Platz EA, Stampfer MJ, et al: JAMA 291:1578-1586, 2004).*

Signs and symptoms

Early-stage disease Men with organ-confined prostate cancer often are completely asymptomatic. Men with a large component of benign prostatic hyperplasia often present with bladder outlet obstruction unrelated to their prostate cancer.

Locally advanced disease Bladder outlet obstruction is the most common sign of locally advanced prostate cancer. A few men with locally advanced disease present with hematuria, urinary tract infections, and irritative voiding symptoms secondary to bladder outlet obstruction.

Advanced disease Rarely, men with bulky lymph node metastasis may present with bilateral lower extremity edema. Men with bony metastasis often present with bone pain and, uncommonly, with lower extremity weakness or paralysis from spinal cord compression.

Screening and diagnosis

Prostate cancer screening with PSA and digital rectal examination (DRE) has resulted in not only an increase in prostate cancer detection but also a stage shift. More cancers are now being detected at earlier stages, when they are potentially curable. Prior to screening efforts, most prostate cancers were detected when they produced local symptoms or distant metastases, at which point treatment for cure often was impossible.

The optimal threshold to recommend prostate biopsy has come under increasing scrutiny. Because the likelihood of confirming a patient's prostate cancer status is to some degree based upon the result of his PSA test, use of PSA as a screening tool is subject to verification bias. Recently, investigators examined prostate biopsy results from a prostate cancer screening cohort and found that a 4.1 ng/mL threshold for biopsy would miss 82% of cancers in men < age 60 and 65% of cancers in older men. The authors concluded that a lower threshold for prostate biopsy is warranted *(Punglia RS, D'Amico AV, Catalona WJ, et al: N Engl J Med 349:335-342, 2003).*

Digital rectal examination Prostate biopsy prompted by abnormal findings on DRE, such as nodularity or induration of the prostate, leads to a diagnosis of prostate cancer in only 15%-25% of cases. This rate compares with a prostate cancer prevalence of < 5% among men of similar age without an abnormal DRE. Although neither accurate nor sensitive for prostate cancer detection, abnormal DRE is associated with a fivefold increased risk of cancer present at the time of screening.

PSA has revolutionized prostate cancer screening. PSA is a serine protease produced by the prostatic epithelium and secreted in the seminal fluid in large quantities. Prostatic disease changes the cellular barriers that normally keep PSA within the ductal system of the prostate and thereby alters serum levels. The level of PSA in serum is increased by inflammation of the prostate, urinary retention, prostatic infection, benign prostatic hyperplasia, prostate cancer, and prostatic manipulation. Although PSA has good sensitivity, it is not an ideal test because an elevated PSA level is neither specific to prostate cancer nor does it distinguish aggressive prostate cancers from those that are biologically benign. Of those patients with a PSA level of > 4.0 ng/mL, approximately 15%-25% will have a diagnosis of prostate cancer.

In the Prostate Cancer Prevention Trial, among 2,950 men who never had a PSA level > 4 ng/mL or an abnormal rectal examination, 449 (15%) had prostate cancer at the time of biopsy, although only 67 (2%) had a Gleason score of 7 or higher. These data suggest that for the purposes of detection, a threshold of 4 ng/mL may not be ideal for prompting subsequent evaluation/biopsy; however, the clinical significance of prostate cancers identified in this subset of men remains uncertain (*Thompson IM, Pauler DK, Goodman PJ, et al: N Engl J Med 350:2239-2246, 2004*).

Current screening recommendations The American Cancer Society and the American Urological Association (AUA) recommends that the PSA test and the DRE should be offered annually beginning at age 50 to men who have a life expectancy of at least 10 years. In high-risk men (African Americans and those with a first-degree relative diagnosed with prostate cancer), screening should be offered at an earlier age (40-45 years old). Prior to testing, physicians should discuss with their

The primary objective of the Prostate Cancer Prevention Trial was to describe the prevalence of histologically proven prostate cancer among men randomized to receive daily finasteride (a 5-alpha-reductase inhibitor that decreases prostate size and serum/prostate dihydrotestosterone levels) or placebo. The authors described a 24.8% reduction in the prevalence of prostate cancer among men taking finasteride, suggesting that it either prevents or delays the appearance of prostate cancer. The caveat of their findings, however, was that these cancers that developed in the treatment arm were of a higher grade *(Thompson IM, Goodman PJ, Tangen CM, et al: N Engl J Med 349:215-224, 2003).*

patients the potential benefits of early prostate cancer detection and its implications in the need for subsequent treatment so that patients can make an informed decision about undergoing screening.

There are currently two ongoing major prostate cancer screening trials: The Prostate, Lung, Colorectal, and Ovarian (PLCO) trial in the United States funded by the National Cancer Institute and the European Organization for Research and Treatment of Cancer (EORTC) trial.

Biopsy When indicated, prostate biopsy usually is performed as an office procedure by transrectal ultrasonographic guidance using an automated 18-gauge biopsy gun. The procedure is performed with, at most, local anesthesia and carries a risk of significant infection of only 1 in 200 cases. Additional side effects of hematuria and hematochezia are common for 2-3 days following the biopsy. Hematospermia may last for up to 2-3 weeks. Since about the year 2000, prostate biopsy includes laterally directed extended core protocols employing 8–12 biopsy cores per procedure. Multiple studies have demonstrated that the addition of the lateral cores improves the accuracy of biopsies.

If the biopsy result is negative, these men are typically followed conservatively with serial PSA levels and DRE repeated annually. Repeat biopsy is performed only when PSA levels rise at abnormal rates (> 0.8 ng/mL/year) or if DRE findings show new nodularity or induration. Men in whom high-grade prostatic intraepithelial neoplasia is found on biopsy usually will be recommended to undergo repeat biopsy, since one-third to one-half will be found to have prostate cancer.

One caveat to PSA screening is its lack of specificity when the value lies between 4 and 10 ng/mL, since many men with benign prostatic hyperplasia have PSA levels in this range. There have been several attempts to increase testing specificity, including the development of age-specific ranges, trends in PSA increase over time (PSA velocity), and calculations of the PSA density based on the volume of the prostate gland. A commonly employed test to increase testing specificity in this "indeterminate zone" is the percent-free PSA. Currently, biopsy is generally recommended in men whose percent-free PSA (ratio of free to total PSA) is < 10%, whereas biopsy is not necessary when percent-free PSA is > 25%. Complexed PSA (cPSA) can also be measured and is now a US Food and Drug Administration (FDA)-approved screening test. It is essentially the "non-free" component of PSA in the circulation and may provide a slight improvement in sensitivity and specificity.

Pathology

Adenocarcinomas make up the vast majority of prostate carcinomas. A total of 70% of prostate adenocarcinomas occur in the peripheral zone, 20% in the transitional zone, and approximately 10% in the central zone.

Other tumor types are relatively rare and include ductal adenocarcinoma, which occurs in the major ducts and often projects into the urethra; and mucinous adenocarcinoma, which secretes abundant mucin and does not arise from the major ducts. Transitional carcinoma of the prostate occurs within the ducts and, to a lesser extent, in the prostatic acini. Typically, primary transitional carcinomas are aggressive cancers that have a poor prognosis. Similarly, neuroendocrine (small-cell) tumors are rare and aggressive, have a poor prognosis, and typically require aggressive surgical management.

Histologic grade The grading system developed by Gleason from data accumulated by the Veterans Administration Cooperative Urologic Research Group appears to provide the best prognostic information in addition to clinical stage and is the predominant grading system in widespread use.

Metastatic spread Adenocarcinoma of the prostate may spread locally through direct extension into periprostatic fat or via the ejaculatory ducts into seminal vesicles; lymphatically to regional lymph nodes, including the hypogastric and obturator lymph nodes; and hematogeneously to bone. The most common sites of bony metastases are the lumbosacral spine (probably related to venous drainage of the prostate through Baston's plexus) and the axial skeleton, but any bone, including the skull and ribs, can be involved. Rare sites of metastatic spread include the liver and lungs.

Staging systems The most widely used and universally accepted staging system for prostate cancer is the TNM system (Table 1). In the TNM system, T1 and T2 tumors are confined to the gland, whereas T3 and T4 tumors have local extension.

Risk-adapted staging The development of the "Partin Tables" in 1993 ushered in a new era of combining clinical stage, Gleason score, and PSA level to predict pathologic stage after radical prostatectomy. More recently, this has led to the D'Amico et al risk groupings for newly diagnosed men with clinically localized disease (Table 2). Patients are divided into three risk groups (low, intermediate, or high) of occult micrometastases and relapse after initial local therapy. Although not perfect, this system is currently in widespread use and allows a framework for multimodal and multidisciplinary treatment strategies based on risk grouping.

A cohort of 223 men with clinically localized disease followed expectantly in Sweden (mean follow-up of 21 years). Substantial declines in disease progression-free, metastasis-free, and prostate-specific survivals were demonstrated in years 15 to 20 of follow-up. Between the two time intervals (0 to 15 years vs 15 to 20 years), the prostate cancer mortality rates increased from 15/1,000/year to 44/1,000/year ($P = .01$), suggesting that treatment should be principally directed at patients with a life expectancy > 15 years *(Johansson JE, Andren O, Andersson SO, et al: JAMA 291:2713-2719, 2004).*

TABLE 1: Staging of prostate cancer

TNM system[a]	
Localized disease	
T1a	Tumor incidental histologic finding in ≤ 5% of resected tissue; not palpable
T1b	Tumor incidental histologic finding in > 5% of resected tissue
T1c	Tumor identified by needle biopsy (eg, because of elevated PSA level)
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
Local extension	
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Bladder invasion, fixed to pelvic side wall, or invasion of adjacent structures
Metastatic disease	
N1	Positive regional lymph nodes
M1	Distant metastasis

[a] Adapted from Greene FI, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

TABLE 2: D'Amico et al risk stratification for clinically localized prostate cancer

Low risk	Diagnostic PSA < 10.0 ng/mL *and* Highest biopsy Gleason score ≤ 6 *and* Clinical stage T1c or T2a
Intermediate risk	Diagnostic PSA > 10 but < 20 ng/mL *or* Highest biopsy Gleason score = 7 *or* Clinical stage T2b
High risk	Diagnostic PSA > 20 ng/mL *or* Highest biopsy Gleason score ≤ 8 *or* Clinical stage T2c/T3

PSA = prostate-specific antigen

In 2003, D'Amico et al combined a number of national datasets to report 10-year cancer-specific mortality for men undergoing radical prostatectomy or external-beam radiotherapy by this risk grouping and age at diagnosis. These 10-year mortality graphs are useful to counsel contemporary-era men contemplating surgery or radiation therapy.

TABLE 3: Risk of dying from clinically localized prostate cancer without definitive locoregional therapy*

	Age			
Gleason score	**55-59**	**60-64**	**65-69**	**70-74**
2-4	4%	5%	6%	7%
5	6%	8%	10%	11%
6	18%	23%	27%	30%
7	70%	62%	53%	42%
8-10	87%	81%	72%	60%

Adapted from Albertsen PC, Hanley JA, Gleason DF, et al: JAMA 280:975–980, 1998.

* Gleason score 7 is now divided between 3 + 4 = 7 (better prognosis) and Gleason score 4 + 3 = 7 (worse prognosis), but the data as in this table are not available for these subgroups at this time.

Prognosis and natural history

Prognosis of untreated prostate cancer Survival depends on patient age at diagnosis, overall health, and tumor grade and stage at diagnosis. The natural history of prostate cancer is becoming increasingly better understood as long-term data become available.

Among untreated patients with clinically localized prostate cancer, those with a low Gleason score (2-4) have a very small risk of dying of their cancer within 15 years (4%-7%), regardless of their age at diagnosis. Those with poorly differentiated tumors (Gleason score 8-10) have a greater risk of dying from prostate cancer than from any other cause, even when the cancer is diagnosed in the eighth decade of life. Indeed, a 55- to 59-year-old man diagnosed with a clinically localized, Gleason score 8-10 prostate cancer has an 87% risk of succumbing to the disease within 15 years if untreated (Table 3).

Treatment

Treatment needs to be individualized. Decisions regarding treatment options are often based on the disease stage and grade, pretreatment PSA level, and rate of PSA level rise, as well as the patient's age and life expectancy. Most recently, prostate biopsy quantification is also an important factor. Specifically, counting the number of involved needle biopsy cores or the percentage of each core involved with cancer is a key prognostic factor. In particular, physiologic age (ie, the presence or absence of other significant medical problems) is of greater importance than chronologic age, and patients with short life expectancy (eg, < 10 years) may well be observed if they have early prostate cancer.

TREATMENT OF CLINICALLY LOCALIZED DISEASE (T1, T2)

Radical prostatectomy

Radical prostatectomy can be performed retropubically through a lower midline incision—an approach that may include pelvic lymph node dissection. Alternatively, some urologists prefer the perineal approach. With the latter approach, a separate incision is required if lymph node removal is desired. Compared with patients managed with watchful waiting, those treated with radical prostatectomy have a lower risk of distant metastases and improved disease-specific survival, although no benefit in overall survival as yet been demonstrated.

Although the morbidity of radical prostatectomy was a major concern in the past, improvements were made during the 1980s. The hazards of anesthesia, risk of blood loss, and hospital stay have all been minimized. Nationwide, Medicare data suggest that surgical outcomes are significantly better at those centers performing > 40 prostatectomies per year than at other hospitals with lower surgical volume.

Transfusion is usually unnecessary, and treatment-related mortality is < 0.05% at leading prostate cancer centers. The average hospital stay of a man undergoing radical prostatectomy is now approximately 2 to 3 days at leading referral centers in the United States; several institutions routinely discharge patients within 24 hours. Although urinary incontinence is common in the first few months after prostatectomy, most men recover urinary control; at some leading centers, 90%-98% of men report few or no long-term urinary problems.

Nerve-sparing radical prostatectomy is appropriate for men with small-volume disease. It offers those men with good potency prior to surgery the probability of recovering that function following the operation. By permitting better visualization of Santorini's dorsal venous plexus, the apical prostate, the urethra, and the striated urethral sphincter, the nerve-sparing technique also reduces blood loss and improves recovery of urinary continence. In appropriately selected individuals, a nerve-sparing procedure confers no greater risk of prostate cancer recurrence after considering other relevant clinical information (PSA, Gleason score, margin status, seminal vesicle involvement, and the presence of extraprostatic spread).

A large study using sildenafil (Viagra) in the postradical prostatectomy setting was reported by Raina and colleagues from the Cleveland Clinic. Specifically, 174 of 470 men (37%) who had undergone surgery sought treatment for erectile dysfunction and were prescribed sildenafil. The response rate was strongly associated with use of nerve-sparing procedures: 76% response in the bilateral nerve-sparing group; 53.5% in the unilateral nerve-sparing group; and 14.2% in the non-nerve-sparing group. Furthermore, preoperative sexual function and age (younger than 65) were strong predictors of efficacy of the oral therapy (*Raina R, Lakin M, Agarwal A, et al: Urology 63:960-966, 2004*).

Referral centers have reported that 50%-90% of patients who are fully potent prior to surgery recover erections following a nerve-sparing procedure, but the quality of these recovered erections may be compromised compared with preoperative erections. Erection recovery rates can be higher than 50% in patients < 60 years of age and lower in

older men. Potency may return anywhere from 2-24 months following surgery. Regardless of potency, sensation of the penis is not changed after this procedure, and men still experience orgasm. Nerve-sparing radical prostatectomy has been shown not to compromise cancer control outcomes in well-selected men with early-stage disease. Also, a recent study has suggested that early postoperative use of sildenafil (Viagra) may facilitate the return of natural erections more quickly.

Evidence among 1,095 men with localized prostate cancer suggests that those with a higher preoperative PSA velocity (> 2 ng/mL in this study) were at greater risk of death from prostate cancer after radical prostatectomy than those with more indoldent PSA velocities, highlighting the role of such an indicator in predicting the aggressiveness of the disease (*D'Amico AV, Chen MH, Roehl KA, et al: N Engl J Med 351:125-135, 2004*).

Laparoscopic radical prostatectomy

Laparoscopic prostatectomy was initially described by Schuessler in 1997 but was abandoned because of its technical difficulty and long operative time with little apparent benefit to the patient over the conventional technique. A recent resurgence in the technique was prompted by improved instrumentation and refinements in the procedure itself, although the laparoscopically naive urologist must endure a substantial learning curve (with attendant perioperative morbidity realized by the patient) prior to meeting the outcome standards set by the open technique.

The robotic assisted prostatectomy was developed to overcome some of the difficulties of the standard laparoscopic prostatectomy (eg, intracorporeal suturing). The robotic technique allows for three-dimensional visualization of the operative field and provides for a significantly wider range of movements intracorporeally than do standard laparoscopic instruments. This advance has prompted the assimilation of the technique into the armamentarium of many urologists.

Current evidence suggests that in experienced hands, the laparoscopic and robotic techniques have similar oncologic efficacy to that of the open procedure. However, the length of follow-up (usually < 12 months) in these studies is limited, suggesting that a measure of caution be taken when interpreting the results. Importantly, long-term effects of these modalities on sexual and urinary health (as measured by a psychometrically valid survey) have not been reported, and such data are critical in the context of the prostatectomy patient when evaluating technical results. Though it is a promising advance in the treatment of prostate cancer, published data suggest further research in this area is warranted.

Pelvic lymph node dissection Studies now indicate that regional pelvic lymph node dissection may not be necessary for patients with stage T1c disease if the total Gleason score is < 7 and the PSA level is < 10.0 ng/mL, ie, low-risk individuals. Selected intermediate-risk men may also not require this staging procedure, but in high-risk men, it is still considered imperative.

Recently, Stephenson et al reported the outcome of 501 patients treated with salvage radiotherapy for increasing PSA levels after radical prostatectomy at five US academic institutions. Although preradiotherapy PSA values had risen to a median of 0.72 ng/mL, 45% of patients had undetectable PSA values 4 years after radiotherapy. Patients lacking adverse risk factors (a Gleason score of 8 or higher, preradiotherapy PSA level > 2.0 ng/mL, negative surgical margins, PSA doubling time < 10 months, and seminal vesicle invasion) achieved a 77% rate of undetectable PSA levels at 4 years, and salvage rates were significantly lower when adverse features were present. These data suggest that earlier salvage therapy is optimal while PSA values are still as low as possible (*Stephenson AJ, Shariat SF, Zelefsky MJ, et al: JAMA 291:1325-1332, 2004*).

Neoadjuvant hormonal therapy

Approximately 35% of men who undergo radical prostatectomy for clinical stage T2 prostate cancer will be found to have pathologic T3 disease following surgery. This finding led some investigators to evaluate the efficacy of neoadjuvant androgen deprivation therapy in prospective clinical trials. Early data from these trials suggested that neoadjuvant hormonal therapy led to a reduction in positive surgical margins. However, these findings need to be considered in a technical context: Androgen deprivation therapy causes artifactual changes in prostate morphology that cause difficulties for the pathologic identification of prostate cancer foci.

Indeed, more recent data from prospective studies have shown no benefit of neoadjuvant therapy with regard to disease progression-free survival. At present, therefore, it appears that neoadjuvant hormonal therapy does not improve the curative potential of radical prostatectomy but instead is associated with morphologic alterations that complicate the prognostic utility of standard pathology. Consequently, neoadjuvant hormonal therapy should be reserved for evaluation as an experimental modality in the context of clinical trials.

Adjuvant therapy post prostatectomy

The potential indications for adjuvant therapy following radical prostatectomy in patients with clinical T1 or T2 malignancy include pathologic evidence of T3 disease, positive nodes, a rising PSA level, and positive surgical margins, among others. Possible adjunct treatments include radiation therapy and androgen deprivation with or without radiation therapy. Best available evidence suggests that early salvage radiotherapy (eg, postprostatectomy PSA level < 0.1 ng/mL) affords the best results in terms of subsequent biochemical recurrence.

Radiation therapy Men with pathologic T3 disease following radical prostatectomy are candidates for adjuvant therapy. However, to date, no prospective randomized trials have demonstrated a survival benefit from adjuvant radiotherapy in patients with pathologic T3 adenocarcinoma of the prostate. At the ASCO 2004 meeting, Bolla et al presented preliminary data from a European trial, randomized between observation and external beam radiation therapy (EBRT) to the prostate bed for pT3 disease after surgery. At a median follow-up of approximately 4 to 5 years, the men randomized to receive EBRT showed a clinical disease-free benefit, but no disease-specific or overall survival difference was evident.

Hormonal therapy Significant controversy exists within the academic community as to the timing of initiating androgen deprivation following radical prostatectomy. Clinical trials have documented a benefit only for those patients with nodal involvement.

The first published report to examine the use of hormonal therapy (HT) for prostate-specific antigen (PSA)-only or biochemical recurrence after radical prostatectomy was authored by Moul et al. Using the Center for Prostate Disease Research (CPDR) multicenter database, the authors studied 1,352 men who had PSA recurrence potoperatively, comparing 355 men who received HT with 997 who were observed. For men with high-risk disease, including a PSA doubling time of < 12 months or a Gleason score of 8 or higher, early HT before the PSA level reached 10 ng/mL was an independent predictor of delayed clinical metastases. Although this is the first study to show a benefit to early HT in this setting, the study was not randomized, and longer follow-up is needed (*Moul J, Wu H, Sun L, et al: J Urol 171:1141-1147, 2004*).

Treatment recommendations for postprostatectomy recurrence

Following radical prostatectomy, it is expected that serial PSA levels will become undetectable. Any detectable PSA level (> 0.2 ng/mL) following surgery indicates possible recurrent disease and the need for restaging and discussion of possible salvage therapies with the patient, including radiation or hormonal therapy, experimental protocols, or observation. However, some patients can develop low levels of detectable PSA after prostatectomy without developing a cancer recurrence, even if no additional treatment is administered. Although there is concern for recurrence when the PSA level is > 0.2 ng/mL, most clinicians will wait until a PSA threshold > 0.4 ng/mL is reached to assume that the rise in PSA level represents real recurrence.

Definitive radiation therapy

External-beam treatment Traditional EBRT is designed to encompass the prostate and, for those at high risk of regional metastasis, the pelvic lymph nodes. A four-field axial box arrangement with customized shielding of normal structures is commonly used. A recently presented study suggests that treatment of regional lymphatics may be beneficial in patients at risk for harboring lymph node metastases.

RTOG 9413 was designed to test the addition of whole pelvic radiotherapy and the timing of androgen deprivation in the treatment of high-risk patients (lymph node-positive potential of > 15% or locally advanced [Gleason score ≥ 6 and > cT2c] cancers). At a median follow-up of 59.5 months, the authors noted an advantage in 4-year disease progression-free survival (60%) among those receiving whole pelvic radiotherapy in conjunction with neoadjuvant androgen deprivation when compared with other treatment arms (44%-50%; *Roach III M, DeSilvio M, Lawton C, et al: J Clin Oncol 21:1904-1911, 2003*).

Conformal EBRT creates three-dimensional representations of target structures (ie, the prostate) and designs highly tailored treatment portals using unconventional treatment directions to create a volume of high radiation dose that conforms to the target shape. The anatomic information used to define the target is generally derived from CT images obtained while the patient is placed in the precise treatment position.

Early results using conformal therapy showed a reduction in acute and early morbidity. Also,

RTOG 92-02 was designed to test the utility of long-term (24 months) androgen blockade compared with short-term (4 months) deprivation among men with locally advanced prostate cancer (T2c-T4). Among all randomized subjects, there was no overall survival benefit among those treated with long-term blockade. A secondary analysis demonstrated that a subset of men with a Gleason score of 8-10 experienced a survival benefit with long-term deprivation (81% vs 71% survival at 5 years, *P* = .04; *Hanks GE, Pajak TF, Porter A, et al: J Clin Oncol 21:3972-3978, 2004*).

conformal therapy has permitted the use of doses far above traditional levels without significant increases in serious morbidity. Patients with relatively low-risk disease (ie, PSA level ≤ 10 ng/mL and Gleason score ≤ 6) generally have a 5-year rate of freedom from disease progression of ~85% when treated with conformal EBRT.

Intensity-modulated radiotherapy (IMRT) is becoming widely used for prostate cancer treatment. This refinement of conformal therapy employs highly nonuniform beam intensity profiles to create more conformal dose distributions. Although it is likely that IMRT will have a greater benefit in the treatment of nonprostate neoplasms (ie, head and neck cancers), there is emerging evidence that prostate cancer therapy is also an appropriate site for IMRT treatment.

EBRT dose The current standard radiotherapy dose is 70 Gy given over 7-8 weeks; however, trials examining the value of dose escalation now support higher doses in selected patients. A randomized trial of EBRT dose compared 70 Gy given conventionally with 78 Gy given with a conformal therapy boost. It showed an advantage in freedom from failure for the higher dose arm that appeared to be limited to those patients with a pretreatment PSA level > 10 ng/mL, whereas no benefit was detected for those with a PSA level < 10 ng/mL. Toxicity was modest but somewhat higher in the higher dose arm. A large trial being conducted by the RTOG (P0126) will accrue 1,520 cases and provide the definitive information regarding any beneficial effect on mortality with higher radiotherapy doses.

Interstitial radiotherapy In the 1970s, the use of permanently placed radioactive iodine implants produced initial results as good as other available radiotherapy techniques and posed a small risk of impotence and other morbidity when compared with conventional EBRT and radical prostatectomy. However, ultimate control rates were unacceptable. The technique used (freehand placement during laparotomy) was found to distribute the radioactive seeds unevenly throughout the gland, and, thus, cold regions may have contributed to the relatively poor outcome.

The use of transrectal ultrasonography to guide seed placement from a transperineal approach has corrected the problem of poor seed placement when performed in experienced hands. Also, radioactive palladium seeds have been developed to increase the dose rate. (Palladium has a shorter half-life than iodine.) Currently, both iodine and palladium implants are used, sometimes in conjunction with EBRT.

Long-term results with improved implant techniques are becoming available, and early results are encouraging for a select population. A large multi-institu-

tion trial compared the results of radical prostatectomy, radiation therapy, and interstitial radiotherapy in men with low-, intermediate-, and high-risk prostate cancer. Brachytherapy was equivalent to the two traditional modalities in terms of PSA recurrence rates for low-risk patients. However, the rates of recurrence were significantly higher in those men with intermediate- and high-risk cancers (specifically, men with a Gleason score ≥ 7 or a PSA level > 10 ng/mL). A typical dose used for interstitial iodine therapy is 145 Gy delivered to the periphery of the prostate. The dose is lower for palladium implants due to the higher dose rate.

Brachytherapy is widely perceived to be less morbid than radical prostatectomy or EBRT in the treatment of localized prostate cancer. However, emerging evidence suggests that some of these benefits may be lost when used as part of a multimodal regimen, as may be necessary in more aggressive disease. In a consecutive series of 177 patients, 44% of those treated with interstitial radiotherapy and EBRT underwent at least one unplanned procedure, such as transurethral resection of the prostate (15%), colonoscopy (36%), fecal diversion (7%), and urinary diversion (3%), suggesting that morbidity may be relatively common in selected patients (*Sarosdy MF: Cancer 22:754-760, 2004*).

High-dose–rate (HDR) devices Besides permanent implants, which deliver low-dose–rate (LDR) radiotherapy, brachytherapy for prostate cancer has been delivered using temporary high-dose–rate devices, usually in patients with locally advanced disease. In this technique, a high dose (minimum, approximately 5 Gy) is delivered to the prostate over ≤ 1 hour by remotely inserting a highly radioactive source into catheters placed into the prostate under ultrasonographic guidance while the patient is under anesthesia. Several treatments are given on separate occasions, and EBRT is used for approximately 5 weeks as well.

More reports are accumulating on the application of HDR brachytherapy to prostate cancer. Various dose-fractionation combinations of HDR with or without combined pelvic EBRT have been employed, with a dose-response relationship apparent in biochemical control. Although the follow-up is short and no prospective randomized trials evaluating this approach have yet been published, it appears that HDR prostate brachytherapy in combination with pelvic EBRT may be effective. The long-term consequences for normal tissue of delivering large doses per fraction using this technique are unclear.

For low-risk men, most experts favor brachytherapy alone to balance the efficacy and side effects of treatment. Specifically, potency rates are generally considered better with brachytherapy alone. However, some centers recommend combined brachytherapy plus EBRT for low-risk men as an assurance of cancer control, but side effects will be greater. At most centers, intermediate-risk and high-risk men are generally offered brachytherapy plus EBRT.

MEDICATIONS AND DEVICES TO MANAGE IMPOTENCE AFTER PROSTATECTOMY, EBRT, OR BRACHYTHERAPY

Treatments for postprostatectomy impotence Treatment for postprostatectomy impotence includes the phosphodiesterase inhibitors sildenafil, vardenafil (Levitra), and tadalafil (Cialis); prostaglandin E_1, administered as a urethral suppository

D'Amico et al evaluated the association between post-treatment PSA doubling time (PSA-DT) and prostate cancer-specific mortality in 8,669 patients treated with surgery or radiotherapy and found a significant association with disease-specific and overall survival. Men with a post-treatment PSA-DT of up to 3 months were particularly likely to develop distant metastasis and die of prostate cancer. The authors propose that post-treatment PSA-DT may be an acceptable surrogate end point for prostate cancer-specific mortality in future clinical trial designs (*D'Amico AV, Moul JW, Carroll PR, et al: J Natl Cancer Inst 95:1376-1383, 2003*).

(Muse); intercavernosal injection (Caverject, Edex); or vacuum-pump erection aids that are useful for improving erections in men who have poor erectile function after prostatectomy, radiation therapy, or brachytherapy. These therapies are effective in 15%-40% of men with postprostatectomy impotence and in 50%-75% of men with postradiotherapy erectile dysfunction. Insertion of a penile prosthesis is typically offered to patients only after unsuccessful trials with the previously mentioned, less invasive interventions.

DETECTION AND TREATMENT OF RECURRENCE

Significance and definition of a rising PSA level post irradiation

The use of PSA levels following definitive therapy (either radiotherapy or radical prostatectomy) can detect early recurrences that may be amenable to salvage treatment. A rising PSA profile following radiotherapy is unequivocal evidence of the presence of a residual prostatic neoplasm. However, the definition of a rising PSA level after radiation therapy varies in the literature. A 1996 consensus conference recommended that PSA failure be considered to have occurred after three consecutive PSA level rises, with the rate of failure defined as halfway between the first rise and the previous PSA level.

Moreover, patients with a rising PSA level after irradiation may be a heterogeneous group, including patients with truly localized failure as well as those with metastatic disease. Also, certain patients will have a slowly rising PSA level after irradiation and may not require additional treatment. In patients who do not receive androgen ablation, the 5-year actuarial risk of distant metastasis from the time that the PSA level begins to rise is ~50%. A rapidly emerging key concept in rising PSA levels is PSA velocity, or more specifically PSA doubling time (PSA-DT). Multiple recent studies have found that a PSA-DT < 10-12 months predicts early clinical relapse if biochemical recurrence is untreated.

Treatment recommendations for recurrence post irradiation

In general, men who have clear evidence of a rising PSA level 2 years after definitive radiotherapy for localized prostate cancer should be advised about the options of hormonal therapy (see section on "Treatment of locally advanced disease [T3, T4]"), salvage surgery, salvage cryotherapy, observation, or experimental therapy.

If patients have minimal comorbidity, good life expectancy, and only local evi-

dence of disease recurrence, salvage surgery is an option but should be preceded by a bone scan, CT scan, cystoscopy, and extensive counseling because urinary difficulties after salvage prostatectomy are substantial and highly prevalent.

TREATMENT OF LOCALLY ADVANCED DISEASE (T3, T4)

The treatment of patients with locally advanced prostate cancer is centered on a multimodality and multidisciplinary approach, including radiation therapy (EBRT with or without HDR interstitial therapy), androgen ablation plus EBRT, or radical prostatectomy with or without androgen deprivation.

EBRT with and without HDR interstitial therapy For patients with locally extensive prostate cancer, local failure remains a potential problem after EBRT. This problem has prompted investigations into alternative means to intensify therapy.

One strategy has been to deliver large fractions of radiotherapy using HDR interstitial techniques in combination with EBRT. The large interstitial fractions, which may be on the order of 5 Gy, deliver a high dose to the prostate but spare normal tissues, due to the rapid dose falloff outside the implanted volume. Early experience with this strategy is encouraging, but long-term data on outcome, particularly in patients with locally extensive disease, and on morbidity are awaited.

Patients with locally advanced prostate cancer probably are not good candidates for permanent prostate implants. Patients with stage T3-T4 tumors are at high risk of gross extraprostatic involvement, and this localized therapy may not offer adequate dosimetric coverage of extraprostatic disease.

Androgen ablation with EBRT Recently, two potential benefits of the use of transient androgen ablation prior to EBRT have been identified. First, there may be some synergy between the apoptotic response induced by androgen deprivation and radiotherapy that may increase local control.

Second, androgen deprivation results in an average 20% decrease in prostate volume. This volume reduction not only may reduce the number of target cells, and thereby improve tumor control, but also may shrink the prostate and, thus, diminish the volume of rectum and bladder irradiated during conformal therapy. Complete androgen blockade can be achieved with the luteinizing hormone-releasing hormone (LHRH) agonists leuprolide (Lupron) or goserelin (Zoladex) plus flutamide (Eulexin), bicalutamide (Casodex), or nilutamide (Nilandron).

The survival benefits of androgen suppression therapy (AST) for intermediate-risk prostate cancers have been uncertain. A recent single-institution, prospective trial randomized patients with a PSA level > 10 ng/mL, a Gleason score ≥ 7, or radiographic evidence of extraprostatic disease to receive EBRT (70 Gy) alone or the same EBRT with 6 months of AST. After a median follow-up of 4.5 years, patients treated with combined EBRT and AST were found to have improved disease progression-free survival ($P = .002$), prostate cancer-specific survival ($P = .02$), and overall survival ($P = .04$). Although 3 years of hormone therapy has been shown to be beneficial in more locally advanced cases, this new trial in men with more localized disease shows a benefit to shorter duration of hormone therapy (*D'Amico AV, Manola J, Loffredo M, et al: JAMA 292:821-827, 2004*).

In addition, since distant metastases are the first manifestation of disease recurrence in many patients with prostate cancer, the use of early androgen deprivation may possibly delay, or even prevent, the development of metastatic disease.

The current body of evidence (RTOG [Radiation Therapy Oncology Group] 8610, RTOG 9202, EORTC [European Organization for Research on the Treatment of Cancer]/Bolla) suggests that androgen deprivation in conjunction with EBRT improves survival among men with locally advanced prostate cancer when compared with radiotherapy alone. Ongoing (eg, RTOG 9413) and future studies will address questions regarding the timing of androgen deprivation and the applicability of androgen deprivation in localized prostate cancers with favorable prognostic features.

Radical prostatectomy with or without adjuvant therapy

Surgical monotherapy can be considered a reasonable option for patients with locally advanced prostate cancer. Stage T3 disease can be successfully treated with low morbidity and significant reductions in risk of local recurrence, with clinical overstaging (up to 26%) reported by Yamada et al. Well- and moderately differentiated cancers have cancer-specific survival rates of 76% at 10 years, comparable to those of other treatment modalities.

The Mayo Clinic has one of the largest radical prostatectomy series for T3 disease, consisting of more than 1,000 patients. In this population, of whom 34% received adjuvant therapy, 15-year cancer-specific survival and local recurrence rates were 77% and 21%, respectively. Ninety-eight men who were found to have nodal metastases following radical prostatectomy and pelvic lymphadenectomy were randomized to receive immediate androgen deprivation or be followed until clinical disease progression. At a median follow-up of 7 years, 18 of 51 men in the observation group had died, compared with only 4 of 47 in the treatment group ($P = .02$).

Treatment of node-positive disease

Until recently, the standard of care had been to perform frozen-section pathologic analysis on pelvic lymph nodes at the time of radical prostatectomy, prior to removal of the prostate. If this analysis revealed micrometastases, radical prostatectomy was thought to be contraindicated. Although retrospective in nature, recent data from several American centers, including one large study from the Mayo Clinic, have reported a survival benefit in men who undergo radical prostatectomy despite the presence of micrometastases to regional pelvic lymph nodes. These men tend to do better and survive longer when started on early hormonal therapy, either with orchiectomy or an LHRH agonist.

Radiation therapy Whether any local treatment adds to the overall survival duration in patients with known nodal involvement is debatable. Some data from M. D. Anderson Cancer Center indicate a benefit from pelvic and prostate radiotherapy plus androgen ablation compared with androgen ablation alone. This matter deserves further study. However, the addition of radiotherapy may be indicated in many situations, especially in young men.

TABLE 4: Hormonal approaches to the treatment of metastatic prostate cancer

Method	Mechanism of action	Side effects
Surgical castration	Removal of testicular androgens	Hot flashes (50%), psychological effects
Diethylstilbestrol (DES)	Inhibition of gonadotropin secretion	Gynecomastia, cardiovascular risks at high doses
LHRH analogs (goserelin, leuprolide)	Inhibition of gonadotropin secretion	Hot flashes (50%), less gynecomastia than DES, fatigue
Antiandrogens (bicalutamide, flutamide, nilutamide)	Blockage of binding of dihydrotestosterone to its receptor	Abnormal liver function studies, diarrhea (10%)

LHRH = luteinizing hormone-releasing hormone

TREATMENT OF ADVANCED SYSTEMIC DISEASE

First-line therapies for advanced disease

The medical treatment of prostate cancer begins when a patient has either not responded to local treatment efforts or presents with advanced disease that cannot be treated effectively with surgery or radiation therapy.

First-line therapy for advanced disease is surgical or medical castration.

Bilateral orchiectomy The testes normally produce approximately 95% of the testosterone in human males, and bilateral orchiectomy reduces plasma testosterone levels by approximately 93%. Although there are other ways besides castration to lower serum testosterone levels (primarily through the estrogen action of LHRH analogs), bilateral orchiectomy has distinct advantages. They include the lack of compliance problems or the need to adjust the dose to the patient's metabolic state and the absence of the potentially fatal cardiovascular complications that are often seen with high-dose estrogen therapy (Table 4). Medical treatment also must be maintained for life and can be very costly. The psychological impact of castration is severe, however, and many men opt for medical therapy if given a choice.

LHRH analogs LHRH agonists, such as leuprolide (in 1- 3-, and 4-month depot formulations and in a 12-month implant) and goserelin (in a 1- and 3-month depot implant), regulate the release of LH and thereby produce chemical castration. These agents spare the patient the psychological trauma of an orchiectomy and also are devoid of the cardiovascular side effects associated with estrogen treatment (Table 4).

Because LHRH analogs can cause a transient increase in testosterone levels and induce a "flare" response, an antiandrogen, such as flutamide, bicalutamide, or nilutamide, is utilized during the first month of LHRH therapy.

A recent review of national practice pattern trends in androgen deprivation for localized prostate cancer was performed employing a longitudinal, observational cohort. The authors noted a significant rise in the use of androgen deprivation between 1989 and 2001 both as primary and neoadjuvant treatments for localized prostate cancer. The use of primary androgen deprivation rose from 4.6% to 14.2% for low-risk patients and from 32.8% to 48.2% for high-risk patients. The authors offered potential reasons for these increases, including financial incentives, consumer-directed marketing, and a "psychological imperative" to treat the cancer *(Cooperberg MR, Grossfeld GD, Lubeck DP, et al: J Natl Cancer Inst 95:981-989, 2003).*

A pure LHRH antagoinst (abarelix [Plenaxis]) has been approved by the FDA. Its main advantage is the lack of an LHRH surge or flare, and it is indicated in men with impending spinal cord compression or other now uncommon clinical scenarios where a flare could be harmful. However, this drug must be administered every 2 weeks in the first month and monthly thereafter. Also, it can rarely be associated with an anaphylactic reaction.

Antiandrogens block the effects of androgens at the prostate tissue level. These compounds appear to interfere with the binding of the active metabolite of testosterone, dihydrotestosterone, to its receptor within the prostate.

In the United States, the most commonly used antiandrogens are flutamide, bicalutamide, and nilutamide. Ketoconazole (Nizoral), an antifungal agent, is also used. As previously mentioned, antiandrogens are added to LHRH analogs to block any transient stimulation of testosterone by these agents or to directly block any remaining androgens that may affect the prostate.

Combined androgen blockade Surgical or medical castration decreases circulating testosterone levels by 90%-95%. It has been demonstrated that the remaining androgens result from peripheral conversion of adrenal steroids. Several investigators have suggested that complete androgen blockade (CAB) or total androgen blockade (TAB), achieved by adding flutamide (250 mg PO tid), bicalutamide (50 mg PO daily), or nilutamide (150 mg PO daily) to castration, results in better disease control.

Although controversial, CAB is most likely beneficial only in patients with minimal symptoms and minimal disease on bone scan. Patients who present with widespread advanced disease and/or poor performance status do not appear to benefit from this approach. A recent meta-analysis showed a modest but statistically significant survival benefit in patients with stage M1 (D2) disease.

Diethylstilbestrol (DES) Estrogen administration, in the form of DES, also produces chemical castration. DES inhibits prostate growth, primarily through the inhibition of the hypothalamic-pituitary-gonadal axis, which blocks testicular synthesis of testosterone and thus lowers plasma testosterone levels. Since doses higher than 3 mg/d cause significant cardiovascular mortality, DES has fallen out of favor as a first-line therapy to induce castration.

Treatment recommendations A patient who presents with advanced prostate cancer requires medical or surgical castration. Although this option has not definitely been demonstrated to increase the patient's life span, the quality-of-

TABLE 5: The incidence of complications from advanced prostate cancer with immediate vs deferred androgen deprivation

Complication	Immediate	Deferred
Pathologic fracture	2.3%	4.5%
Spinal cord compression	2.0%	5.0%
Ureteric obstruction	7.0%	11.8%
Extraskeletal metastases	7.9%	11.8%

life benefits gained from disease control are unquestioned. Controversy exists over whether to start treatment early, when a patient is still asymptomatic, or whether to wait until symptoms develop. However, it is generally accepted that treatment should begin early. The primary goal of early androgen deprivation should be prolongation of survival or prevention of catastrophic consequences of advanced disease (Table 5).

In patients with minimal bone involvement (usually defined as fewer than five lesions) and minimal symptoms, CAB is the treatment of choice. It can be accomplished by orchiectomy or the use of depot injections of leuprolide (7.5 mg SC monthly) or goserelin (3.6 mg SC monthly). Further androgen blockade is accomplished by the addition of an antiandrogen, such as flutamide (250 mg PO tid), bicalutamide (50 mg PO daily), or nilutamide (150 mg PO daily).

Patients presenting with widespread bone or soft-tissue disease can be treated with surgical castration alone. If medical castration therapy is used, treatment with an antiandrogen for 1 month after the initiation of castration therapy is recommended. This can be accomplished with flutamide, bicalutamide, nilutamide, or ketoconazole (400 mg PO tid). For men with advanced disease such as spinal cord compression, where a flare could be clinically detrimental, the pure LHRH agonist aberelix is appropriate.

Recently, the efficacy of bicalutamide monotherapy (150 mg/d) compared with flutamide plus goserelin was tested in a randomized study of patients with histologically proven C or D disease. Fewer patients in the bicalutamide group experienced loss of libido ($P = .01$) and erectile dysfunction ($P = .002$). Significant trends also were noted in the bicalutamide-treated patients with respect to their quality of life and social functioning, vitality, emotional well-being, and physical capacity. Bicalutamide monotherapy was as effective as traditional androgen deprivation therapy for patients with nonmetastatic disease at a median follow-up of about 7 years. However, in patients with stage D (M1) disease, bicalutamide monotherapy provided a slight survival disadvantage (median 45 days shorter survival) than traditional androgen deprivation therapy.

Bicalutamide (150 mg) monotherapy has also been tested as adjuvant therapy after radical prostatectomy and EBRT and with watchful waiting A clinical

disease-free benefit has been observed, but a survival benefit has not yet been demonstrated.

Second-line hormonal therapies

Initial hormone ablation controls symptoms for 2 to 5 years in the average contemporary patient wtih minimal metastatic disease. In the past, patients typically presented with new urinary symptoms or new bone pain while receiving castration treatment, but with the advent of PSA determinations, most of these patients can be identified by a rising PSA level prior to symptom onset. It is unclear whether these patients should be treated immediately or whether therapy should be delayed until the onset of symptoms.

Several strategies have been employed as secondary hormonal treatments. In general, responses are seen in about 20% of patients and usually last approximately 6 months.

Addition or subtraction of an antiandrogen If a patient has been receiving monotherapy, an antiandrogen is typically added, but responses are seen in only about 10% of patients. In patients who have been treated with CAB, omitting the antiandrogen from the regimen can cause a paradoxical shrinkage of measurable disease, a decrease in serum PSA level, and/or a lessening of symptoms in 10%-25% of patients. Thus, the addition or subtraction of the antiandrogen has become the next step for patients in whom initial hormone

TABLE 6: Chemotherapy regimens for prostate cancer

Drug/combination	Dose and schedule
Mitoxantrone/prednisone	
Mitoxantrone	12 mg/m^2 IV on day 1
Prednisone	5 mg PO bid
Repeat cycle every 21 days.	
Tannock IF, Osoba D, Stockler MR, et al: J Clin Oncol 14:1756–1764, 1996.	
Docetaxel/estramustine	
Docetaxel	60 mg/m^2 on day 2 every 21 days
Estramustine	280 mg orally on days 1 to 5 every 21 days
Dexamethasone	60 mg orally given as a premedication before docetaxel
Petrylak DP, Tangen CM, Hussain MHA, et al: N Engl J Med 351:1513–1520, 2004.	
Docetaxel/prednisone	
Docetaxel	75 mg/m^2 IV every 3 weeks
Prednisone	5 mg orally twice daily started on day 1
Note: Standard docetaxel premedication should be given prior to the administration of docetaxel	
Tannock IF, de Wit R, Berry WR, et al: N Engl J Med 351:1502–1512, 2004.	

Table prepared by Ishmael Jaiyesimi, DO

therapy is ineffective. If this measure fails, another second-line agent is often employed.

Aminoglutethimide (Cytadren) and hydrocortisone have been widely used. Aminoglutethimide is started at a dose of 125 mg PO qid and increased to 250 mg PO qid. It is associated with significant side effects, including lethargy, weakness, rash, and fever.

Hydrocortisone (20 mg PO bid) alone affords significant pain relief, as well as occasional objective tumor responses.

Ketoconazole, with or without hydrocortisone, is also used. Ketoconazole is started at a dose of 200 mg PO tid and then escalated to a total dose of 400 mg tid. The 1,200-mg daily dose is associated with nausea and vomiting, however, and can result in severe liver injury. Patients receiving high-dose ketoconazole need to be monitored carefully for signs and symptoms of liver damage, and the drug should be stopped immediately if liver enzyme levels become elevated.

Petrylak and colleagues from the Southwest Oncology Group (SWOG) reported on 770 men with Hormone-refractory prostate cancer (HRPC) randomized to receive mitoxantrone (Novantrone) plus prednisone vs docetaxel (Taxotere) plus estramustine (Emcyt) plus dexamethasone. The docetaxel arm had improved survival by a median of 2 months, showing for the first time that a chemotherapy drug could extend survival in HRPC. A second trial by Eisenberger et al showed a similar survival benefit of docetaxel with prednisone given on an every-3-week schedule. (*Petrylak D, Tangen C, Hussain M, et al: N Engl J Med 351:1513-1520, 2004*).

Chemotherapy for hormone-refractory disease

Despite the effectiveness of initial hormonal therapy, metastatic prostate cancer is an incurable disease, with patients surviving a median of 16 months.

One recent advance is the acceptance of PSA levels as a surrogate marker for response in hormone-refractory prostate cancer. Currently, a PSA level decline of < 50% from pretreatment baseline that persists for at least 4 weeks is considered a partial response in clinical trials. Although not proven in a phase III setting, utilization of PSA levels has helped identify new, potentially active chemotherapy regimens for use in patients with advanced androgen-independent disease (Table 6).

Mitoxantrone (Novantrone) plus prednisone The combination of mitoxantrone and prednisone has been approved for use in patients with hormone-refractory prostate cancer who are experiencing pain. Mitoxantrone (12 mg/m^2 IV) is administered every 3 weeks. Prednisone is given as a 10-mg oral daily dose (5 mg bid). Toxicities of the combination include leukopenia and thinning of the hair.

Bisphosphonates for advanced prostate cancer

Bisphosphonates inhibit osteoclast activation. In a recent study, it was demonstrated that zoledronic acid (Zometa) significantly decreased pain associated with bone metastases as well as fractures in patients undergoing chemotherapy for hormone-refractory prostate cancer. Zoledronic acid has been approved by the FDA for use in patients with skeletal metastases and hormone-refractory prostate cancer.

Radiation therapy for palliating bone metastasis

Radiotherapy is effective in controlling local pain associated with skeletal prostate metastasis. In general, a treatment regimen of 30 Gy over 10 treatments results in rapid and durable local symptom control and a reduced dependence on analgesics.

For patients with more extensive bone involvement causing pain that may be difficult to address with localized EBRT, alternatives include wide-field irradiation (ie, hemibody irradiation) or systemic administration of radioactive bone-seeking isotopes that can deliver therapeutic doses to skeletal metastatic disease. Radioactive isotopes used in this fashion include strontium-89 chloride (Metastron) and samarium SM 153 lexidronam (Quadramet). A more detailed discussion of these approaches can be found in chapter 37.

SUGGESTED READING

Albertsen PC, Hanley JA, Gleason DF, et al: Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 280:975–980, 1998.

Crook JM, Szumacher E, Malone S, et al: Intermittent androgen suppression in the management of prostate cancer. Urology 53:530–534, 1999.

D'Amico AV, Whittington R, Malkowicz SB, et al: Biochemical outcome after radical prostatectomy, external-beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 280:969–974, 1998.

D'Amico AV, Chen MH, Roehl KA, et al: Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med 351:125–135, 2004.

D'Amico AV, Moul JW, Carroll PR, et al: Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. J Clin Oncol 21:2163–2172.

D'Amico AV, Moul JW, Carroll PR, et al: Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. J Natl Cancer Inst 95:1376–1383, 2003.

Hellerstedt BA, Pienta KJ: The current state of hormonal therapy for prostate cancer. CA Cancer J Clin 52:154–179, 2002.

Holmberg L, Bill-Axelson A, Helgesen F, et al: A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med 347:781–789, 2002.

Johansson JE, Andren O, Andersson SO, et al: Natural history of early, localized prostate cancer. JAMA 291:2713–2719, 2004.

Sarosdy MF: Urinary and rectal complications of contemporary permanent transperineal brachytherapy for prostate carcinoma with or without external beam radiation therapy. Cancer 22:754–760, 2004.

Stephenson AJ, Shariat SF, Zelefsky MJ, et al: Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 291:1325–1332, 2004.

Thompson IM, Pauler DK, Goodman PJ, et al: Prevalence of prostate cancer among men with a prostate-specific antigen level < or = 4.0 ng per milliliter. N Engl J Med 350:2239–2246, 2004.

Yao SL, Lu-Yao G: Population-based study of relationships between hospital volume of prostatectomies, patient outcomes, and length of hospital stay. J Natl Cancer Inst 91:1950–1956, 1999.